ARANESP®
(darbepoetin alfa)
For Injection

DESCRIPTION

Aranesp™ is an erythropoiesis stimulating protein closely related to erythropoietin that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp™ is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3.[1] The 2 additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Aranesp™ is formulated as a sterile, colorless, preservative-free protein solution for intravenous (IV) or subcutaneous (SC) administration.

Single-dose vials are available containing either 25, 40, 60, 100, or 200 mcg of Aranesp™. Two formulations contain excipients as follows:

Polysorbate solution contains 0.05 mg polysorbate 80, 2.12 mg sodium phosphate monobasic monohydrate, 0.66 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (per 1 mL) at pH 6.2 ± 0.2.

Albumin solution contains 2.5 mg albumin (human), 2.23 mg sodium phosphate monobasic monohydrate, 0.53 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (per 1 mL) at pH 6.0 ± 0.3.

CLINICAL PHARMACOLOGY

Mechanism of Action

Aranesp™ stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with progenitor stem cells to increase red cell production. Production of endogenous erythropoietin is impaired in patients with chronic renal failure (CRF), and erythropoietin deficiency is the primary cause of their anemia. Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with Aranesp™.

Pharmacokinetics

Aranesp™ has an approximately 3-fold longer terminal half-life than Epoetin alfa when administered by either the IV or SC route.

Following IV administration to adult CRF patients, Aranesp™ serum concentration-time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and mean terminal half-life of approximately 21 hours.

Following SC administration, the absorption is slow and rate-limiting, and the terminal half-life is 49 hours (range: 27 to 89 hours), which reflects the absorption half-life. The peak concentration occurs at 34 hours (range: 24 to 72 hours) post-SC administration in adult CRF patients, and bioavailability is approximately 37% (range: 30% to 50%).

The distribution of Aranesp™ in adult CRF patients is predominantly confined to the vascular space (approximately 60 mL/kg). The pharmacokinetic parameters indicate dose-linearity over the therapeutic dose range. With once weekly dosing, steady-state serum levels are achieved within 4 weeks with < 2-fold increase in peak concentration when compared to the initial dose. Accumulation was negligible following both IV and SC dosing over 1 year of treatment.

CLINICAL STUDIES

The safety and effectiveness of Aranesp™ have been assessed in multicenter studies. Two studies evaluated the safety and efficacy of Aranesp™ for the correction of anemia in adult patients with CRF, and 2 studies assessed the ability of Aranesp™ to maintain hemoglobin concentrations in adult patients with CRF who had been receiving other recombinant erythropoietins.

De Novo Use of Aranesp®

In 2 open-label studies, Aranesp™ or Epoetin alfa were administered for the correction of anemia in CRF patients who had not been receiving prior treatment with exogenous erythropoietin. Study 1 evaluated CRF patients receiving dialysis; Study 2 evaluated patients not requiring dialysis (predialysis patients). In both studies, the starting dose of Aranesp™ was 0.45 mcg/kg administered once weekly. The starting dose of Epoetin alfa was 50 U/kg 3 times weekly in Study 1 and 50 U/kg twice weekly in Study 2. When necessary, dosage adjustments were instituted to maintain hemoglobin in the study target range of 11 to 13 g/dL. (Note: The recommended hemoglobin target is lower than the target range of these studies. See DOSAGE AND ADMINISTRATION: General for recommended clinical hemoglobin target.) The primary efficacy endpoint was the proportion of patients who experienced at least a 1.0 g/dL increase in hemoglobin concentration to a level of at least 11.0 g/dL by 20 weeks (Study 1) or 24 weeks (Study 2). The studies were designed to assess the safety and effectiveness of Aranesp™ but not to support conclusions regarding comparisons between the 2 products.

In Study 1, the hemoglobin target was achieved by 72% (95% CI: 62%, 81%) of the 90 patients treated with Aranesp™ and 84% (95% CI: 66%, 95%) of the 31 patients treated with Epoetin alfa. The mean increase in hemoglobin over the initial 4 weeks of Aranesp™ treatment was 1.10 g/dL (95% CI: 0.82 g/dL, 1.37 g/dL).

In Study 2, the primary efficacy endpoint was achieved by 93% (95% CI: 87%, 97%) of the 129 patients treated with Aranesp™ and 92% (95% CI: 78%, 98%) of the 37 patients treated with Epoetin alfa. The mean increase in hemoglobin from baseline through the initial 4 weeks of Aranesp™ treatment was 1.38 g/dL (95% CI: 1.21 g/dL, 1.55 g/dL).

Conversion From Other Recombinant Erythropoietins

Two studies (Studies 3 and 4) were conducted in adult patients with CRF who had been receiving other recombinant erythropoietins and compared the abilities of Aranesp™ and other erythropoietins to maintain hemoglobin concentrations within a study target range of 9 to 13 g/dL. (Note: The recommended hemoglobin target is lower than the target range of these studies. See DOSAGE AND ADMINISTRATION: General for recommended clinical hemoglobin target.) CRF patients who had been receiving stable doses of other recombinant erythropoietins were randomized to Aranesp™, or to continue with their prior erythropoietin at the previous dose and schedule. For patients randomized to Aranesp™, the initial weekly dose was determined on the basis of the previous total weekly dose of recombinant erythropoietin. Study 3 was a double-blind study conducted in North America, in which 169 hemodialysis patients were randomized to treatment with Aranesp™ and 338 patients continued on Epoetin alfa. Study 4 was an open-label

study conducted in Europe and Australia in which 347 patients were randomized to treatment with Aranesp™ and 175 patients were randomized to continue on Epoetin alfa or Epoetin beta. Of the 347 patients randomized to Aranesp™, 92% were receiving hemodialysis and 8% were receiving peritoneal dialysis.

In Study 3, a median weekly dose of 0.53 mcg/kg Aranesp™ (25^{th}, 75^{th} percentiles: 0.30, 0.93 mcg/kg) was required to maintain hemoglobin in the study target range. In Study 4, a median weekly dose of 0.41 mcg/kg Aranesp™ (25^{th}, 75^{th} percentiles: 0.26, 0.65 mcg/kg) was required to maintain hemoglobin in the study target range.

INDICATIONS AND USAGE

Aranesp™ is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis.

CONTRAINDICATIONS

Aranesp™ is contraindicated in patients with:

- uncontrolled hypertension
- known hypersensitivity to the active substance or any of the excipients

WARNINGS

Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin

Aranesp™ and other erythropoietic therapies may increase the risk of cardiovascular events, including death, in patients with CRF. The higher risk of cardiovascular events may be associated with higher hemoglobin and/or higher rates of rise of hemoglobin.

In a clinical trial of Epoetin alfa treatment in hemodialysis patients with clinically evident cardiac disease, patients were randomized to a target hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL.[2] Higher mortality (35% versus 29%) was observed in the 634 patients randomized to a target hemoglobin of 14 g/dL than in the 631 patients assigned a target hemoglobin of 10 g/dL. The reason for the increased mortality observed in this study is unknown; however, the incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

In CRF patients the hemoglobin should be managed carefully, not to exceed a target of 12 g/dL.

In patients treated with Aranesp™ or other recombinant erythropoietins in Aranesp™ clinical trials, increases in hemoglobin greater than approximately 1.0 g/dL during any 2-week period were associated with increased incidence of cardiac arrest, neurologic events (including seizures and stroke), exacerbations of hypertension, congestive heart failure, vascular thrombosis/ischemia/infarction, acute myocardial infarction, and fluid overload/edema. It is recommended that the dose of Aranesp™ be decreased if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period, because of the association of excessive rate of rise of hemoglobin with these events.

Hypertension

Patients with uncontrolled hypertension should not be treated with Aranesp™; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anemia with Aranesp™ or Epoetin alfa. In Aranesp™ clinical trials, approximately

40% of patients required initiation or intensification of antihypertensive therapy during the early phase of treatment when the hemoglobin was increasing. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with Aranesp™ or Epoetin alfa.

Special care should be taken to closely monitor and control blood pressure in patients treated with Aranesp™. During Aranesp™ therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by pharmacologic or dietary measures, the dose of Aranesp™ should be reduced or withheld (see DOSAGE AND ADMINISTRATION: Dose Adjustment). A clinically significant decrease in hemoglobin may not be observed for several weeks.

Seizures

Seizures have occurred in patients with CRF participating in clinical trials of Aranesp™ and Epoetin alfa. During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of Aranesp™ be decreased if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period.

Albumin (Human)

Aranesp™ is supplied in 2 formulations with different excipients, one containing polysorbate 80 and another containing albumin (human), a derivative of human blood (see DESCRIPTION). Based on effective donor screening and product manufacturing processes, Aranesp™ formulated with albumin carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

General

A lack of response or failure to maintain a hemoglobin response with Aranesp™ doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid or vitamin B_{12} should be excluded or corrected. Intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis may compromise an erythropoietic response.

The safety and efficacy of Aranesp™ therapy have not been established in patients with underlying hematologic diseases (eg, hemolytic anemia, sickle cell anemia, thalassemia, porphyria).

Hematology

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Aranesp™ before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to prevent the hemoglobin from exceeding the recommended target (12 g/dL) or rising too rapidly (greater than 1.0 g/dL in 2 weeks), the guidelines for dose and frequency of dose adjustments should be followed (see DOSAGE AND ADMINISTRATION: Dose Adjustment).

Patients With CRF Not Requiring Dialysis

Patients with CRF not yet requiring dialysis may require lower maintenance doses of Aranesp™ than patients receiving dialysis. Though predialysis patients generally receive less frequent monitoring of blood pressure and laboratory parameters than dialysis patients, predialysis patients may be more responsive to the effects of Aranesp™, and require judicious monitoring of blood pressure and hemoglobin. Renal function and fluid and electrolyte balance should also be closely monitored.

Dialysis Management

Therapy with Aranesp™ results in an increase in red blood cells and a decrease in plasma volume, which could reduce dialysis efficiency; patients who are marginally dialyzed may require adjustments in their dialysis prescription.

Laboratory Tests

After initiation of Aranesp™ therapy, the hemoglobin should be determined weekly until it has stabilized and the maintenance dose has been established (see DOSAGE AND ADMINISTRATION). After a dose adjustment, the hemoglobin should be determined weekly for at least 4 weeks until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment, as the majority of patients will eventually require supplemental iron therapy. Supplemental iron therapy is recommended for all patients whose serum ferritin is below 100 mcg/L or whose serum transferrin saturation is below 20%.

Information for Patients

Patients should be informed of the possible side effects of Aranesp™ and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their Aranesp™ treatment, dietary and dialysis prescriptions, and the importance of judicious monitoring of blood pressure and hemoglobin concentration should be stressed.

If it is determined that a patient can safely and effectively administer Aranesp™ at home, appropriate instruction on the proper use of Aranesp™ should be provided for patients and their caregivers, including careful review of the “Information for Patients and Caregivers” insert. Patients and caregivers should also be cautioned against the reuse of needles, syringes, or drug product, and be thoroughly instructed in their proper disposal. A puncture-resistant container for the disposal of used syringes and needles should be made available to the patient.

Drug Interactions

No formal drug interaction studies of Aranesp™ with other medications commonly used in CRF patients have been performed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity: The carcinogenic potential of Aranesp™ has not been evaluated in long-term animal studies. Aranesp™ did not alter the proliferative response of nonhematological cells in vitro or in vivo. In toxicity studies of approximately 6 months duration in rats and dogs, no

tumorigenic or unexpected mitogenic responses were observed in any tissue type. Using a panel of human tissues, the in vitro tissue binding profile of Aranesp™ was identical to Epoetin alfa. Neither molecule bound to human tissues other than those expressing the erythropoietin receptor.

Mutagenicity: Aranesp™ was negative in the in vitro bacterial and CHO cell assays to detect mutagenicity and in the in vivo mouse micronucleus assay to detect clastogenicity.

Impairment of Fertility: When administered intravenously to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at any doses evaluated (up to 10 mcg/kg/dose, administered 3 times weekly). An increase in postimplantation fetal loss was seen at doses equal to or greater than 0.5 mcg/kg/dose, administered 3 times weekly (3-fold higher than the recommended weekly starting human dose).

Pregnancy Category C

When Aranesp™ was administered intravenously to rats and rabbits during gestation, no evidence of a direct embryotoxic, fetotoxic, or teratogenic outcome was observed at doses up to 20 mcg/kg/day (40-fold higher than the recommended weekly starting human dose). The only adverse effect observed was a slight reduction in fetal weight, which occurred at doses causing exaggerated pharmacological effects in the dams (1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species. No significant placental transfer of Aranesp™ was observed in rats. An increase in postimplantation fetal loss was observed in studies assessing fertility (see Carcinogenesis, Mutagenesis, and Impairment of Fertility: Impairment of Fertility).

Intravenous injection of Aranesp™ to female rats every other day from day 6 of gestation through day 23 of lactation at doses of 2.5 mcg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring.

There are no adequate and well controlled studies in pregnant women. Aranesp™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether Aranesp™ is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Aranesp™ is administered to a nursing woman.

Pediatric Use

The safety and efficacy of Aranesp™ in pediatric patients have not been established.

Geriatric Use

Of the 1598 CRF patients in clinical studies of Aranesp™, 42% were age 65 and over, while 15% were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

In all studies, the most frequently reported serious adverse reactions with Aranesp™ were vascular access thrombosis, congestive heart failure, sepsis, and cardiac arrhythmia. The most commonly reported adverse reactions were infection, hypertension, hypotension, myalgia, headache, and diarrhea (see WARNINGS: Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin/Hypertension). The most frequently reported adverse reactions resulting in clinical intervention (eg, discontinuation of Aranesp™, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were hypotension, hypertension, fever, myalgia, nausea, and chest pain.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Aranesp™ cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

The data described below reflect exposure to Aranesp™ in 1598 CRF patients, including 675 exposed for at least 6 months, of whom 185 were exposed for greater than 1 year. Aranesp™ was evaluated in active-controlled (n = 823) and uncontrolled studies (n = 775).

The rates of adverse events and association with Aranesp™ are best assessed in the results from studies in which Aranesp™ was used to stimulate erythropoiesis in patients anemic at study baseline (n = 348), and, in particular, the subset of these patients in randomized controlled trials (n = 276). Because there were no substantive differences in the rates of adverse reactions between these subpopulations, or between these subpopulations and the entire population of patients treated with Aranesp™, data from all 1598 patients were pooled.

The population encompassed an age range from 18 to 91 years. Fifty-seven percent of the patients were male. The percentages of Caucasian, Black, Asian, and Hispanic patients were 83%, 11%, 3%, and 1%, respectively. The median weekly dose of Aranesp™ was 0.45 mcg/kg (25^{th}, 75^{th} percentiles: 0.29, 0.66 mcg/kg).

Some of the adverse events reported are typically associated with CRF, or recognized complications of dialysis, and may not necessarily be attributable to Aranesp™ therapy. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received Aranesp™ or other recombinant erythropoietins.

The data in Table 1 reflect those adverse events occurring in at least 5% of patients treated with Aranesp™:

Table 1. Adverse Events Occurring in ³ 5% of Patients

Event	Patients Treated With Aranesp ā (n = 1598)
APPLICATION SITE	
Injection Site Pain	7%
BODY AS A WHOLE	
Peripheral Edema	11%
Fatigue	9%
Fever	9%
Death	7%
Chest Pain, Unspecified	6%
Fluid Overload	6%
Access Infection	6%
Influenza-like Symptoms	6%
Access Hemorrhage	6%
Asthenia	5%
CARDIOVASCULAR	
Hypertension	23%
Hypotension	22%
Cardiac Arrhythmias/Cardiac Arrest	10%
Angina Pectoris/Cardiac Chest Pain	8%
Thrombosis Vascular Access	8%
Congestive Heart Failure	6%
CNS/PNS	
Headache	16%
Dizziness	8%
GASTROINTESTINAL	
Diarrhea	16%
Vomiting	15%
Nausea	14%
Abdominal Pain	12%
Constipation	5%
MUSCULO-SKELETAL	
Myalgia	21%
Arthralgia	11%
Limb Pain	10%
Back Pain	8%
RESISTANCE MECHANISM	
Infection[a]	27%

[a] Infection includes sepsis, bacteremia, pneumonia, peritonitis, and abscess.

Continued

Event	Patients Treated With Aranesp® (n = 1598)
RESPIRATORY	
Upper Respiratory Infection	14%
Dyspnea	12%
Cough	10%
Bronchitis	6%
SKIN AND APPENDAGES	
Pruritus	8%

The incidence rates for other clinically significant events are shown in Table 2.

Table 2. Percent Incidence of Other Clinically Significant Events

Event	Patients Treated With Aranesp™ (n = 1598)
Acute Myocardial Infarction	2%
Seizure	1%
Stroke	1%
Transient Ischemic Attack	1%

Thrombotic Events

Vascular access thrombosis in hemodialysis patients occurred in clinical trials at an annualized rate of 0.22 events per patient year of Aranesp™ therapy. Rates of thrombotic events (eg, vascular access thrombosis, venous thrombosis, and pulmonary emboli) with Aranesp™ therapy were similar to those observed with other recombinant erythropoietins in these trials.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Aranesp™ has not been adequately determined. Radioimmunoprecipitation and neutralizing antibody assays were performed on sera from 1534 patients treated with Aranesp™. High-titer antibodies were not detected, but assay sensitivity may be inadequate to reliably detect lower titers. Since the incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may additionally be influenced by several factors including sample handling, concomitant medications, and underlying disease, comparison of the incidence of antibodies to Aranesp™ with the incidence of antibodies to other products may be misleading.

Erythrocyte aplasia, in association with antibodies to erythropoietin, has been reported on rare occasions in patients treated with other recombinant erythropoietins. Due to the close relationship of Aranesp™ to endogenous erythropoietin, such a response is a theoretical possibility with Aranesp™ treatment, but has not been observed to date.

There have been rare reports of potentially serious allergic reactions including skin rash and urticaria associated with Aranesp™. Symptoms have recurred with rechallenge, suggesting a

causal relationship exists in some instances. If an anaphylactic reaction occurs, Aranesp™ should be immediately discontinued and appropriate therapy should be administered.

OVERDOSAGE

The maximum amount of Aranesp™ that can be safely administered in single or multiple doses has not been determined. Doses over 3.0 mcg/kg/week for up to 28 weeks have been administered. Excessive rise and rate of rise in hemoglobin, however, have been associated with adverse events (see WARNINGS and DOSAGE AND ADMINISTRATION: Dose Adjustment). In the event of polycythemia, Aranesp™ should be temporarily withheld (see DOSAGE AND ADMINISTRATION: Dose Adjustment). If clinically indicated, phlebotomy may be performed.

DOSAGE AND ADMINISTRATION

General

Aranesp™ is administered either IV or SC as a single weekly injection. The dose should be started and slowly adjusted as described below based on hemoglobin levels. If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated (see PRECAUTIONS: General/Laboratory Tests). When Aranesp™ therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter.

For patients who respond to Aranesp™ with a rapid increase in hemoglobin (eg, more than 1.0 g/dL in any 2-week period), the dose of Aranesp™ should be reduced (see DOSAGE AND ADMINISTRATION: Dose Adjustment) because of the association of excessive rate of rise of hemoglobin with adverse events (see WARNINGS: Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin).

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin level not to exceed 12 g/dL.

Starting Dose

Correction of Anemia

The recommended starting dose of Aranesp™ for the correction of anemia in CRF patients is 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. Because of individual variability, doses should be titrated to not exceed a target hemoglobin concentration of 12 g/dL (see Dose Adjustment). For many patients, the appropriate maintenance dose will be lower than this starting dose. Predialysis patients, in particular, may require lower maintenance doses. Also, some patients have been treated successfully with a SC dose of Aranesp™ administered once every 2 weeks.

Conversion From Epoetin alfa to Aranesp ã

The starting weekly dose of Aranesp™ should be estimated on the basis of the weekly Epoetin alfa dose at the time of substitution (see Table 3). Because of individual variability, doses should then be titrated to maintain the target hemoglobin. Due to the longer serum half-life, Aranesp™ should be administered less frequently than Epoetin alfa. Aranesp™ should be administered once a week if a patient was receiving Epoetin alfa 2 to 3 times weekly. Aranesp™ should be administered once every 2 weeks if a patient was receiving Epoetin alfa once per week. The route of administration (IV or SC) should be maintained.

Table 3. Estimated Aranesp® Starting Doses (mcg/week) Based on Previous Epoetin alfa Dose (Units/week)

Previous Weekly Epoetin alfa Dose (Units/week)	Weekly Aranesp® Dose (mcg/week)
< 2,500	6.25
2,500 to 4,999	12.5
5,000 to 10,999	25
11,000 to 17,999	40
18,000 to 33,999	60
34,000 to 89,999	100
≥ 90,000	200

Dose Adjustment

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin not to exceed 12 g/dL.

Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, doses should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1.0 g/dL in a 2-week period, the dose should be decreased by approximately 25%.

If the increase in hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate (see PRECAUTIONS: Laboratory Tests), the dose of Aranesp™ may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

Maintenance Dose

Aranesp™ dosage should be adjusted to maintain a target hemoglobin not to exceed 12 g/dL. If the hemoglobin exceeds 12 g/dL, the dose may be adjusted as described above. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient.

Preparation and Administration of Aranesp®

1. Do not shake Aranesp™. Vigorous shaking may denature Aranesp™, rendering it biologically inactive.
2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
3. Do not dilute Aranesp™.
4. Do not administer Aranesp™ in conjunction with other drug solutions.

5. Aranesp™ is packaged in single-use vials and contains no preservative. Discard any unused portion. Do not pool unused portions.

6. See the accompanying "Information for Patients and Caregivers" leaflet for complete instructions on the preparation and administration of Aranesp™.

HOW SUPPLIED

Aranesp™ is available in 2 solutions, an albumin solution and a polysorbate solution. The words "Albumin Free" appear on the polysorbate container labels and the package main panels as well as other panels as space permits. Aranesp™ is available in the following packages:

1 mL Single-dose Vial, Polysorbate Solution

1 Vial/Pack, 4 Packs/Case	**4 Vials/Pack, 10 Packs/Case**
200 mcg/1 mL (NDC 55513-006-01)	25 mcg/1 mL (NDC 55513-002-04)
	40 mcg/1 mL (NDC 55513-003-04)
	60 mcg/1 mL (NDC 55513-004-04)
	100 mcg/1 mL (NDC 55513-005-04)

1 mL Single-dose Vial, Albumin Solution

1 Vial/Pack, 4 Packs/Case	**4 Vials/Pack, 10 Packs/Case**
200 mcg/1 mL (NDC 55513-014-01)	25 mcg/1 mL (NDC 55513-010-04)
	40 mcg/1 mL (NDC 55513-011-04)
	60 mcg/1 mL (NDC 55513-012-04)
	100 mcg/1 mL (NDC 55513-013-04)

Storage

Store at 2° to 8°C (36° to 46°F). Do not freeze or shake. Protect from light.

REFERENCES

1. Egrie JC and Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). *Brit J Cancer*. 2001;84(Suppl 1):3-10.

2. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339:584-90.

Rx only

This product, or its use, may be covered by one or more US Patents, including US Patent No. 5,618,698, in addition to others including patents pending.

Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799

Issue Date XX/XX/2001